Study Title: Effectiveness of KeraStat Gel for Improved Cosmesis of Partial Thickness Burns

NCT03564795

Summary

This study seeks to determine whether the use of KeraStat Gel as the primary dressing for partial thickness burns (1) results in improved healed wound cosmesis and (2) results in less painful dressing changes, faster reepithelialization, and reduction in need for excision and grafting. The study design is a within subject control. Each of two distinct burns will be randomized to the use of KeraStat Gel or standard of care (SOC). The length of study participation for a subject is 1 year. Subjects complete 2 office visits and 2 remote visits during the first month then office visits at months 3, 6, and 12 post burn.

Subjects will complete a visual analog scale for pain during dressing changes, and the reepithelialization of the wound will be noted. During remote visits on days 7 and 21, subjects may complete a digital VAS scale and collect a photo of the wound. At months 3, 6, and 12, subjects and study personnel will complete the Patient Observer Scar Assessment Scale (POSAS). During month 3, 6, and 12 visits, the scars will be subjected to measurement of transepidermal water loss (TEWL) measured with a Tewameter. The wound sites will be photographed at each site visit.

Background, Rationale and Context

Background

Burn injuries are classified based on depth as either superficial, partial thickness, or full thickness. Partial thickness burns involve damage to deeper structures within the skin (below the epidermis) such as blood vessels, nerves, and hair follicles. Typically, partial thickness burns can heal without surgical intervention. However, without proper wound management (if the wound dries out or becomes infected), partial thickness burns can progress to deep partial thickness or full thickness burns. While a number of wound dressings are available for use on partial thickness burns, conventional dressings can adhere to and disrupt the wound surface, require frequent dressing changes (up to twice daily), and demonstrate limited effectiveness for their ability to support initial burn wound healing and prevent long-term scarring[1,2].

Impaired healing can lead to scarring, which poses functional, aesthetic, and psychological challenges. The lack of effective scar treatment has resulted in a significant need to develop new solutions to control scar formation, prevent contracture, and improve the quality of life for burn victims. Current treatments designed to prevent hypertrophic scar formation include applying silicone sheets or gels over the burn 14 to 21 days post-injury, occlusive dressings, pressure garment therapy for up to 2 years post-injury, silver sulfadiazine, corticosteroids, and treating

[1] Wasiak J, Cleland H, Campbell F. Dressings for superficial and partial thickness burns. *Cochrane Database of Systematic Reviews* 2008, Issue 4.

[2] Dorsett-Martin W., Persons, B, Wysocki A, Lineaweaver W. New topical agents for topical treatment of partial-thickness burns in children: A review of published outcome studies. Published online at woundsresearch.com 2008

existing scars with laser ablation or excision[3,4,5,6,7]. None have shown consistent effectiveness in addressing scarring cosmesis.

Rationale

Ideally, wound dressings for partial thickness burns should absorb fluid, maintain high humidity (i.e., moisture) at the wound site to encourage healing, provide a barrier to prevent infection, and possess mechanical characteristics to accommodate movement[1]. Currently, there are several biopolymer wound dressings available that function in this manner. These products include Collatek Hydrogel, Occulus Microcyn Wound Gel, Phytacare Alginate Hydrogel Wound Dressing, and Keratec Wound Dressing.

KeraStat® Gel is a sterile, non-implantable, water-based gelatinous (hydrogel) wound dressing intended to act as a protective covering in the management of a variety of partial thickness dermal wounds. Keratin is a structural, filamentous protein that, when hydrated, forms a hydrogel that provides coverage and maintains a moist environment for injured skin, similar to collagen and other extracellular matrix molecules used in existing products. Therefore, KeraStat Gel is expected to behave in an equivalent manner to conventional biopolymer wound dressings. ISO 10993 biocompatibility studies and performance testing, both *in vitro* and *in vivo*, indicated that KeraStat Gel is safe and biocompatible. Additionally, two clinical studies support the assertion that the product is non-sensitizing, non-irritating, and does not produce a humoral response. The current study is designed to evaluate the effectiveness of KeraStat Gel in improving scarring cosmesis when topically applied as a primary dressing to human subjects with partial thickness burns. We hypothesize that use of KeraStat Gel, as compared to the standard of care (SOC), will result in improved cosmesis of the healed wounds.

Objectives

The primary objective of the proposed research is to determine whether the use of KeraStat Gel as the primary dressing for partial thickness burns results in improved cosmesis of the healed wounds.

Secondary objectives include determining whether KeraStat Gel wound dressing results in less painful dressing changes, faster reepithelialization, and reduction in need for excision and grafting.

---

[3] Delavary, B.M., et al., Macrophages in skin injury and repair. Immunobiology, 2011. 216(7): p. 753-762.

[4] Tandara, A.A. and T.A. Mustoe, The role of the epidermis in the control of scarring: evidence for mechanism of action for silicone gel. Journal of Plastic Reconstructive and Aesthetic Surgery, 2008. 61(10): p. 1219-1225.

[5] Mustoe, T.A. and A. Gurjala, The role of the epidermis and the mechanism of action of occlusive dressings in scarring. Wound Repair and Regeneration, 2011. 19: p. S16-S21.

[6] Steinstraesser, L., et al., Pressure Garment Therapy Alone and in Combination with Silicone for the Prevention of Hypertrophic Scarring: Randomized Controlled Trial with Intraindividual Comparison. Plastic and Reconstructive Surgery, 2011. 128(4): p. 306E-313E.

[7] Bloemen, M.C.T., et al., Prevention and curative management of hypertrophic scar formation. Burns, 2009. 35(4): p. 463-475.

Methods and Measures

Design

This study is a randomized, controlled, within-subject trial examining the effectiveness of KeraStat Gel, as compared to the institutional SOC, Mepilex Ag, in improving wound cosmesis. Once the Investigator has determined the subject is a candidate for inclusion in the study, the subject will be approached about enrolling in this study. A total of 30 burn subjects presenting to the Burn Centers will be enrolled.

Upon presenting to the hospital, potential study subjects will be assessed for inclusion and approached for consent, as appropriate. Once the subject and/or legal guardian has consented to participate in the study, baseline assessments can be completed. We anticipate that the majority of subjects presenting with burns that qualify for inclusion in the study will have at least one night stay in the hospital; however, this is not criteria for inclusion. KeraStat Gel and Mepilex Ag will each be randomized to application on one of two identified burn sites on the subject, Burn A or Burn B. All subjects will have one burned area dressed with KeraStat Gel and a second area dressed with Mepilex Ag per SOC. The Investigator or study staff will initially apply the dressings per a computer-generated randomization scheme. The burn dressed with KeraStat Gel will have a secondary dressing of petrolatum gauze and telfa. For subjects who have more than two burns, all additional burns will be treated according to the physician's discretion. Subjects will be provided with enough KeraStat Gel and KeraStat Gel-related dressing supplies upon hospital discharge to accommodate prescribed dressing changes until their next visit. The Investigator will instruct subjects on dressing changes as required by institutional SOC guidelines and instructions for use of KeraStat Gel prior to discharge. The need to maintain treatment consistency will be stressed; Burn A and Burn B should always receive their designated dressing.

For the first 4 weeks, subjects will have weekly visits with site staff. On days 7 and 21, this visit will be remote. On days 14, and 28, this visit will be an office visit.

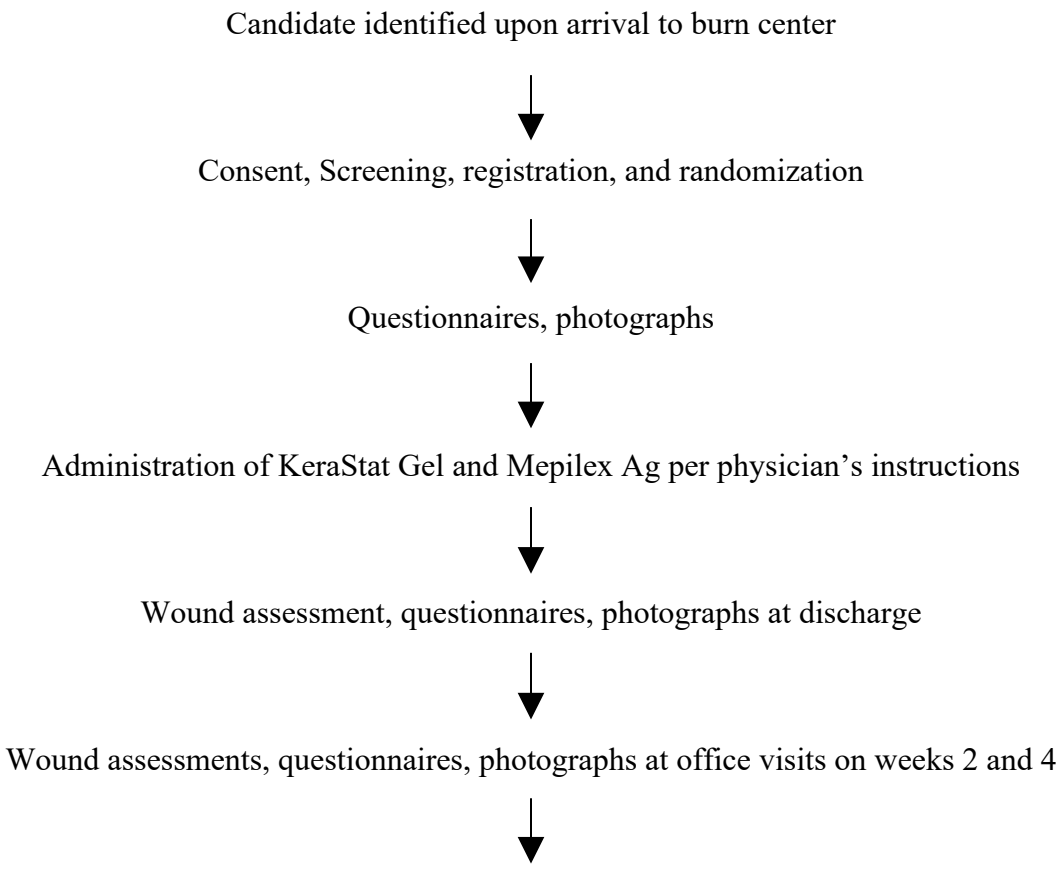
During remote visits, adverse event recording will be recorded by the site. If the subject has agreed to the use of the Engage application on their phone, the subject will also complete a pain assessment for each burned area (Burn A and Burn B). For the Engage application, the subject number will be obtained for registration and completion of the e-diary. The subject will set up a personal identification number (PIN) and provide responses to security questions that will be used if they forget their PIN. The e-diaries will be completed via a web application on the mobile phone that is hosted in a database. As a Software-as-a-Service (SaaS) provider of clinical trial software and services, Clinical Ink acts as an agent on behalf of customers to collect Clinical Study Data. With respect to all Clinical Study Data, the collecting and processing of data are governed by the contractual relationship with each customer consistent with the notice provisions specified by the customer in their relationship with the individuals participating in the clinical study.

If the subject agrees to and is able, the subject will capture photographs of the wounds and upload to the MyChart application. Briefly, the subject will obtain the photograph and navigate to the MyChart application utilizing the web-browser on their phone. The subject should then navigate to the "Messaging" center and click "Ask a Question". From here, the subject selects "New Medical Question." The subject should choose their study physician and mark a "Visit Follow-Up Question". They then can attach an image and click send.

During office visits on days 14 and 28, adverse event recording, incidence of infection, assessment of reepithelialization, photography, and a pain assessment will be completed for each burned area (Burn A and Burn B). A $45 gas card (one per visit) and KeraStat Gel-related dressing supplies will be given to the subject during these visits, as well.

Partial thickness burns that do not require excision and grafting are expected to be fully closed within 21 days. Thus, after assessment at discharge, subjects will be followed bi-weekly until 4 weeks post-burn to ensure appropriate healing. Then, subjects will be seen at 3 months (±7 days), 6 months (±7 days), and 1 year (±14 days) post-enrollment for site photographs and in order to assess the development of scarring using the Patient and Observer Scar Assessment Scale (POSAS), and TEWL measurements.

Below is a schematic overview of the study.



Optional at-home questionnaire and photographs at virtual visits on weeks 1 and 3

Wound assessments, questionnaires, photographs, TEWL assessment at 3 months, 6 months, 1 year

Setting

This study will be conducted in the Wake Forest (WF) Burn Center and in the University Medical Center New Orleans (UMC). Subjects may continue treatment as inpatients or as outpatients.

Subjects Selection Criteria

- **Inclusion Criteria**
  - Males and females, age 6 years and older
  - Written informed consent and assent, if applicable (including parent if subject is a minor)
  - Presenting with at least two comparable, discrete, and separate partial thickness thermal burns, as determined by the Investigator, measuring 50-1,000 cm^2 each
  - Study wounds identified are partial thickness depth
  - KeraStat Gel and Mepilex Ag can be applied to the randomized study burn wounds as definitive care treatment within 72 hours from time of injury
  - Overall total body surface area (TBSA) burned < 20%

- **Exclusion Criteria**
  - Pregnant or nursing
  - Prisoner
  - Presence of inhalation injury, as determined by the Investigator
  - Injury requiring formal intravenous fluid resuscitation
  - Concomitant non-thermal traumatic injuries
  - Chronic medical conditions including, but not limited to, documented renal impairment (Cr > 2.5 mg/dL), hepatic impairment (Total bilirubin > 2.5 mg/dL), thromboembolic disorders, active infection in study wound areas, uncontrolled diabetes (HbA1C > 7%), HIV infection, history of melanoma or systemic malignancy within the last 10 years
  - Receiving corticosteroids, immunosuppressive agents, radiation or chemotherapy, topical growth factors, or any other medication the Investigator feels will affect wound healing
  - Not expected to live at least 13 months post-burn
  - Previously treated with a skin graft at either of the treatment sites

- Chemical or electrical burn
- Proposed study wounds are full thickness
- Any condition the Investigator determines will compromise subject safety or prevent the subject from completing the study

- **Sample Size**
  The study size is 30 subjects, two wounds per subject, 30 wounds per treatment cohort resulting in 60 total wounds.

  Because this trial is designed to examine long-term outcomes, no interim analyses or stopping rules are planned.

Interventions and Interactions

Intervention: KeraStat Gel

Agent description

Ingredients: Water (Aqua), Oxidized Keratin, Carbopol, Phenoxyethanol, Ethylhexylglycerin, and Sodium Hydroxide. KeraStat Gel is for topical use only and should not be swallowed. Subjects should avoid contact with eyes. If swallowed, seek medical attention. If symptoms worsen or persist, consult a physician.

Agent Safety Data

KeraStat Gel has been subjected to a full suite of ISO 10993 safety testing (Table 1).

Table 1. Summary of Completed ISO 10993 Testing

Test [a,b]	Method	Test System	Route	Testing Outcome
Cytotoxicity	ISO 10993-5	Mouse fibroblast CCL-1 (L929)	*In vitro*	Non-cytotoxic
Sensitization	ISO 10993-10	Guinea Pig	Topical *In vivo*	Non-sensitizing
Irritation	ISO 10993-10	Rabbit (NZ White)	Intracutaneous *In vivo*	Mild-Moderate Irritant
Acute Systemic Toxicity (3 day)	ISO 10993-11	Mouse (Swiss Albino)	Intraperitoneal *In vivo*	Non-toxic
Subacute Systemic Toxicity (28 day)	ISO 10993-11	Rat (Albino)	Subcutaneous *In vivo*	Non-toxic

Pyrogenicity	ISO 10993-11	Rabbit (NZ White)	Intravenous *In vivo*	Non-pyrogenic

Performance testing, including *in vivo* testing of its application to burn wounds, supports the safety and reliable quality of this device. Two clinical studies have also supported product safety. This product is approved by the U.S. Food and Drug Administration (FDA) (K162759).

Agent Administration

In this clinical trial, subjects will apply KeraStat Gel as directed by the physician per institutional SOC guidelines. We anticipate that the medical care team or subject will clean and dress the wound every 1 to 3 days. KeraStat Gel should be changed at least every 3 days but can be changed as often as the Investigator feels is necessary. The wound should first be cleansed and debrided according to the institutional SOC guidelines. Following cleansing, KeraStat Gel should be applied uniformly, providing a coating across the entire surface of the burn and past the edge of the burn. On average, one tube of KeraStat Gel will cover 0.5% TBSA. At the time of dressing changes, KeraStat Gel should be removed with soap and water and gauze wiping (as necessary), reapplied, and covered with a secondary dressing of petrolatum gauze. Treatment will continue until full reepithelialization (100%) is achieved.

Interactions
At baseline, demographic and medical history will be collected, and inclusion/exclusion criteria will be confirmed. If the subject meets these criteria, vital signs will be collected, and the wounds will be randomized to treatment including KeraStat Gel dressings or SOC. Two burns identified by the Investigator will be labeled Burn A and Burn B by study staff and noted on the Case Report Form (CRF). The randomization scheme will be generated in nQuery Advisor 7.0 in advance by the study statistician. An adequate, sequentially numbered, opaque, sealed envelope set will be produced prior to the implementation of the protocol for the site to use. These envelopes will be shipped and maintained at the site with the trial staff member designated by the Investigator or the Investigator themselves to conduct randomization. The staff will choose the first envelope in sequence, record the subject ID and date of the randomization on the outside of the envelope. They will open the envelope and reveal the index card with the treatment assignment for Burn A and Burn B, record again the Subject ID and randomization date on that card, and then upload a photo of the completed card with the Subject's source documentation for the clinic visit. No subject may be randomized early into the study. All envelopes at each site must be used in sequential order. Any alterations to this procedure will be considered a protocol violation. Burns will be examined and photographed. The subject will be asked to complete the Visual Analog Scale (VAS) pain score for each burn site on study. Once each treatment is applied, the subject will once again complete the VAS pain score for each burn site. Thus, two VAS pain scores will be collected for each burn at each treatment application by study staff.

Hospital staff will change dressings until the subject is discharged from the hospital. At discharge, the burns will once again be examined and photographed. The subject will be asked

to complete the Visual Analog Scale (VAS) pain score for each burn site on study. Once each treatment is applied, the subject will once again complete the VAS pain score for each burn site. Subjects will be provided with enough KeraStat Gel-related dressings to last 17 days. Subjects will be instructed on dressing changing procedures for both burns per institutional SOC guidelines.

Dressings will be changed per institutional SOC guidelines but at a minimum of every 3 days. Subjects will return to the clinic on days 14 ±3 and 28 ±3 post-enrollment for the first 4 weeks and at months 3 (±7 days), 6 (±7 days), and 12 (±14 days) post-enrollment. Subjects will also participate in a remote visit on days 7±3 and 21 ±3 post-enrollment. Dressing changes will be continued until reepithelialization is achieved. During each visit, study staff will document the number of dressing changes that occurred outside of clinic visits as well as any pertinent information related to the dressing changes. During visits when dressing changes are still necessary, subjects will complete the VAS pain score before and after dressing changes to each burn, and any unanticipated adverse events related to the device will be logged. Subjects who are able and willing will download an application on their smartphone that will prompt them to record the VAS pain score before and after dressing changes will complete this during remote visits on days 7 and 14. Subjects will also be asked to upload photos of the burns at days 7 and 21 utilizing the medical center's MyChart application. Appearance of the sites will be assessed at months 3, 6, and 12 using the POSAS. During the visits at 3, 6, and 12 months, sites will be subjected to 3 measurements of TEWL. Photographs will be obtained at all in-person visits and may be subjected to wound closure and percent epithelialization measurements via ImageJ. Recording of adverse events (AE), measurement of vital signs, examination of the wound/site of wound, and notation of concomitant medication and procedures will also take place during each visit. All measures will be completed if an individual agrees to a final visit after withdrawal from the study.

Masking
This study will be an open-label study.

Schedule of Events

Baseline Testing (All subjects)

- Photographs (prior to start of treatment)
- Vital signs (e.g., blood pressure, heart rate, temperature, height, weight)
- Examination of wound, including wound measurement
- Concomitant medications
- VAS pain score before and after dressing application

Discharge

- Adverse events

- Vital signs
- Examination of wound, including wound measurement and percent reepithelialization
- Photography of treatment site
- Concomitant medications and procedures
- Dressing change
- VAS pain score before and after dressing change

Day 7, 21 (*±3,* ***Remote visit)***

- Photography of treatment site on days 7 and 21 (optional)
- VAS pain score before and after dressing changes (optional)
- Adverse events

Day 14, 28 *(±3)* ***Evaluation***

- Adverse events
- Vital signs
- Examination of wound, including wound measurement and percent reepithelialization
- Photography of treatment site
- Concomitant medications and procedures
- Documentation of number and description of dressing changes since last visit (for subjects who do not participate in the optional tracking)
- Dressing change
- VAS pain score before and after dressing change

3 Month *(±7 days)****, 6 Month*** *(±7 days)****, 1 Year*** *(±14 days)* ***Evaluation***

- Adverse events
- Vital signs
- Examination of wound/site of wound, including wound measurement
- Photography of treatment site
- Concomitant medications and procedures
- POSAS
- TEWL

Early Termination Visit/Withdrawal from Study

- Adverse events
- Vital signs
- Examination of wound, including wound measurement
- Photography of treatment site
- Concomitant medications and procedures

- Dressing change (Month 1)
- VAS pain score before and after dressing change (Month 1)
- POSAS (Months 3-12)
- TEWL (Months 3-12)

Outcome Measure(s)

Assessments	Screening/Day 0	Discharge	Remote Follow-Up (Days 7 ±3 and 21 ±3)	First Month Follow-Up (Days 14 ±3, 28 ±3)	3 Month (±7 day), 6 Month (±7 day), 1 Year (±14 day) Follow-ups	Early Termination Visit
Written Informed Consent	X					
Demographic and Medical History	X					
Inclusion/Exclusion Criteria	X					
Randomization*	X					
Unanticipated Adverse Device Events		X	X	X		X
Adverse Events		X	X	X	X	X
Vital Signs	X	X		X	X	X
Examine Wound/ Site of Wound, including wound measurement	X	X		X	X	X
Photography of Treatment Sites	X	X	X**	X	X	X
Concomitant Medications	X	X		X	X	X
Concomitant Procedures		X		X	X	X
Dressing Changes	As needed	As needed	As needed	As needed		
VAS Pain Score	X	X	X**	X		X
Wound Closure (Investigator assessment)				X		X
Percent epithelialization				X		X

Assessments	Screening/Day 0	Discharge	Remote Follow-Up (Days 7 ±3 and 21 ±3)	First Month Follow-Up (Days 14 ±3, 28 ±3)	3 Month (±7 day), 6 Month (±7 day), 1 Year (±14 day) Follow-ups	Early Termination Visit
(Investigator assessment)						
Cosmesis of Treatment Sites (POSAS)					X	X
TEWL					X	

*Randomization will occur after confirmation of inclusion and exclusion criteria.
**These activities will be optional and dependent on whether subject has resources for use of an at-home application.

The VAS pain score[8] is a simple, widely used instrument that has been utilized for pain assessments since the 1970s. It will be administered by site personnel during a clinic visit. The VAS will also be completed during dressing changes at home on days 7 and 21 by subjects who agree to the use of an at-home phone application. This unidimensional measure is composed of a line, usually 10 centimeters in length, anchored by two verbal descriptors representing the symptom extremes ("no pain" and "worst imaginable pain") and 6 facial expression anchors. The respondent places a line perpendicular to the VAS line that represents their pain intensity. The distance between the "no pain" anchor and the subject's mark is measured in cm, providing a range of scores from 0 to 10.

TEWL[9] has been shown to be strongly correlated with hypertrophic scar values and erythema. It will be measured using a tewameter. The scar area will be measured three times by placing the probe perpendicular without pressure on the area of interest with the surface area in horizontal position. The three individual measurements will be recorded.

The POSAS[8] is a reliable and complete scale that takes into account the judgment of both the subject and the Investigator. It will be administered by site personnel during a clinic visit. The subject form provides space for indicating the scar location and includes seven questions, which are answered using a numerical scale anchored by two verbal descriptors representing the symptom extremes or agreement. Similarly, the observer assessment scale provides space for indicating the location of the scarring. It includes seven parameters that are scored using a numerical scale anchored by two verbal descriptors representing the symptom extremes ("normal skin" to "worst scar imaginable"). These are further described by pre-defined categories.

[8] Fearmoni, R.; Bond, J.; Erdmann, D; Levinson, H. A review of scar scales and scar measuring devices. Eplasty. 2010; 10:e43.
[9] Gardien, K.; Baas, D.; de Vet H.; Middelkoop, E. Transepidermal water loss measured with the Tewameter TM300 in burn scars. Burns. 2016: 42(7):1455-1462.

Photographs will be obtained during each subject contact. Photos will be obtained from a distance of approximately 18 inches (if possible) so as to encompass each burn in its entirety. A ruler will lay flush with adjacent uninjured skin and will be included in each picture. Cameras and downloading capabilities should be tested prior to enrolling the first subject. Only jpeg images taken with a digital camera will be accepted. Photographs are a requirement of participation in this clinical trial. Optional photographs will be collected on days 7 and 21 by subjects who are able and willing to upload photos utilizing the instution's MyChart application.

Additional points:

Baseline photographs must be taken after informed consent but prior to randomization.

Images will be transferred from the site's camera to the patient portal. The file naming convention is Patient Acrostic_Burn ID_Visit Number.

At the visit where complete wound closure is documented, the photographs of the burns may be subjected to analysis using ImageJ to confirm wound closure.

Study Subject Withdrawal

Subjects may withdraw from study participation at any time. Decision to withdraw should be noted on the CRF including the date and reason. Study staff should ask subject if he/she will agree to a final visit, and this should be noted on the CRF as well.

Analytical Plan

Descriptive statistics for continuous variables and frequency counts and percentages for categorical demographics variables will be summarized by subject and by burn treatment group. Listings will be created for all data by Case Report Form. A Statistical Analysis Plan (SAP) that includes mock tables, listings and figures (TLFs) will be developed and finalized prior to the lock of the clinical database. The extent to which missing data occurs will be described with an interpretation of the extent on the impact of the analysis as well as generalizability of the data.

Statistical analyses will be conducted for two analysis populations.

a. Intention to treat: All subjects randomized will be included in the analyses.
b. Safety: All subjects that have received one or more treatment applications will be included in the safety analysis for all safety endpoints.

For the primary objective of the study, improved cosmesis will be analyzed using data from the POSAS, as a total score, and separately for the observer score and then the subject score. Changes from baseline will be examined at 3 months, 6 months and again at 1 year post treatment. TEWL will be considered at 3 months, 6 months, and 1 year. This analysis may also consider the baseline status of the burn including depth, surface area, location of the burn injury and subject baseline characteristics (age, concomitant injury).

Secondary objectives include determining whether KeraStat Gel wound dressing results in less painful dressing changes, faster reepithelialization, and reduction in need for excision and grafting. Improvement in pain will be assessed using the scoring from the VAS pain scale at Screening, Days 7, 14, 21 and 28. Box plots of the VAS pain scores will be presented displaying the medians and quartiles in each treatment group over time. A nonparametric test will be used to determine changes in the score across time (Kruskal-Wallis) as well. Reductions in excision and grafting will be analyzed by treatment groups using the same methods as the VAS pain score. Median time to 100% reepithelialization by study treatment group will be conducted, mean times (days) will be analyzed using a Wilcoxon test by treatment groups, as well as a time to event analysis for 90% or higher reepithelialization from baseline.

The incidence of adverse events will be reported and summarized by treatment group. Adverse events will be coded in MedDRA by system organ class and preferred terms (PT).

Human Subjects Protection

Subject Recruitment Methods
Subjects who present at the Burn Center at WF or UMC with qualifying burns as determined by the Investigator will be approached for inclusion in the study by study personnel.

Remuneration
Enrolled study subjects will be provided with one $45 gas card per visit for office visits on days 14 and 28 and months 3, 6, and 12.

Informed Consent
All subjects must give their informed consent in accordance with the informed consent regulations in Title 21 CFR, Part 50. Each subject over 18 years and subjects under 18 and their legally authorized representative will execute written informed consent (and assent if applicable) before any study procedures are conducted. Study personnel will obtain written informed consent in the clinic.

Confidentiality and Privacy
Confidentiality will be protected by collecting only information needed to assess study outcomes, minimizing to the fullest extent possible the collection of any information that could directly identify subjects, and maintaining all study information in a secure manner. To help ensure subject privacy and confidentiality, only a unique study identifier will appear on the data collection form. Any collected subject identifying information corresponding to the unique study identifier will be maintained on a linkage file and stored separately from the data. The linkage file will be kept secure, with access limited to designated study staff. Following data collection, the subject identifying information will be destroyed consistent with data validation and study design, producing an anonymous analytical data set. Data access will be limited to study staff and Sponsor. Data and records will be kept locked and secured, with any computer

data password protected. No reference to any individual subject will appear in reports, presentations, or publications that may arise from the study. Empiristat will receive de-identified information for statistical analysis. KeraNetics staff may have access to subject files during monitoring. Neither Empiristat nor KeraNetics staff will have direct interaction with study participants.

Data and Safety Monitoring

The Principal Investigator will be responsible for the overall monitoring of the data and safety of study subjects. The Principal Investigator will be assisted by other members of the study staff.

An attempt will be made to follow every subject enrolled in the study through completion. Subjects may go 'off-study' for the following reasons: protocol has been completed, unanticipated AE, serious adverse event (SAE), subject lost to follow-up, non-compliance with study instructions, medical contraindication, subject withdraws consent, or death. If a subject or the Investigator decides that the subject should not complete the study, the reason and circumstances for such early withdrawal must be fully documented. A subject may end his/her participation in the study at any time and without consequence to the subject. The reason(s) the subject goes 'off-study' should be recorded on the CRF. Every attempt should be made to conduct the 12-month visit CRFs, for the termination visit.

The Research Monitor, Dr. Preston R. Miller, III, MD FACS is responsible to oversee the safety of the research and report observations/findings to the IRB or a designated institutional official. The Research Monitor will review all unanticipated problems involving risks to subjects or others associated with the protocol and provide an independent report of the event to the IRB. The Research Monitor may discuss the research protocol with the investigators; shall have authority to stop a research protocol in progress, remove individual human subjects from a research protocol, and take whatever steps are necessary to protect the safety and well-being of human subjects until the IRB can assess the monitor's report; and shall have the responsibility to promptly report their observations and findings to the IRB or other designated official.

Risks and Benefits

There are no known risks associated with using KeraStat Gel. ISO 10993 testing supports the safety of the product. ISO 10993-10 testing suggested that some subjects may experience irritation; however, a GLP preclinical study and a human repeat patch test indicate the product is a non-irritant. A human skin prick test found that the product does not elicit an allergic response. The currently known risks associated with participation in this study include: discomfort at the wound site, infection at the wound site, lack of wound closure, and an allergic reaction to the dressings, sedatives, narcotics, or any other drugs which might be administered concomitantly with the procedure. All subjects will be given information on potential side effects and will be offered the option of alternative treatments by the Investigator prior to enrolling in the study. There may also be other side effects that we cannot predict or are not known. Taking part in this research study may involve providing information that subjects consider confidential or private. Efforts, such as coding research records, keeping research records secure, and allowing only

authorized people to have access to research records, will be made to keep subject information safe.

Alternative treatments include but are not limited to other topical (applied to the skin) dressings, such as silver sulfadiazine or triple antibiotic ointment or saline-soaked gauze.

Subjects will receive the study dressings (i.e., KeraStat Gel and KeraStat Gel-related secondary dressings) at no cost during the study. Based on initial performance testing in animals, burn wounds randomized to receive KeraStat Gel treatment may benefit from improved cosmesis, improved healing rates, reduced fibrosis and contraction, and no increase in infection rates compared to Mepilex Ag. Subjects will also be seen in the clinic regularly for visits and may gain more information about management of their condition. We hope the information learned from this study will benefit burn patients and clinicians in the future.

Subject Benefit to Participation in the Study

There are no identifiable direct benefits to participating in this study. However, there are some *potential* benefits to participation. Given that the burns will be examined more often than what is many times the typical approach, there is a potentially reduced risk of infection. Additionally, there is the potential for more rapid healing of the study burns treated with KeraStat.

Reporting of Unanticipated Problems, Adverse Events or Deviations

Any unanticipated problems, serious and unexpected AEs, deviations, or protocol changes will be promptly reported by the Principal Investigator or designated member of the research team to the Institutional Review Board (IRB) and Sponsor or appropriate government agency if appropriate.

An AE is defined as any unfavorable or unintended change in body structure, body function, laboratory result (*e.g.*, chemistry, ECG), or worsening of a pre-existing condition associated temporally with the use of the test product, whether or not considered related to the test product. All AE will be recorded in the Case Report Form (CRF), and a cumulative total will be evaluated for each subject and across all subjects treated. AE and concomitant medications will be reported based on the MedDRA dictionary and evaluated for relationship to KeraStat Gel or dressing-related procedures. Any AE not requiring intervention will be reported at the discretion of the Investigator. AE, concomitant medications, and vital signs will be monitored and recorded at each study visit. Concomitant procedures will be assessed.

AEs that are anticipated for this subject population include: neurological/psychological, cardiovascular, pulmonary, gastrointestinal, genitourinary, renal, musculoskeletal, blood, endocrine, skin/wound, infectious, eye/ear/nose/throat, chemical, and hematological complications.

While these events may be temporally associated with study participation, they are consistent with severe burns and may not be considered related to the study under most circumstances. An Investigator (to include other qualified study staff) will be responsible for evaluating individual

subjects and determining whether a specific event is potentially study-related or whether the event could be reasonably anticipated as normal sequelae of the subject's clinical status, injury, and hospital course.

In the event of an AE, the Investigator will use accepted institutional SOC guidelines (medical or surgical), as needed. Expected or unexpected AE will be managed according to institutional SOC guidelines.

All subjects will be treated to alleviate signs and symptoms as appropriate medical intervention dictates. All procedures or medical therapies related to treatment of the complication will be recorded. Investigator assessment of reasons for failure and medical/surgical management will be recorded in the CRF. Subjects who are discontinued from study treatment will remain in the study for safety assessments and efficacy analysis.

All AE will be recorded on the CRF. The time of the onset, location, duration, intensity, relationship to the test product, treatment, and follow-up will also be captured on the CRF. The relationship between the application of KeraStat Gel and the AE will be determined by the Investigator as 'not related' or 'related'. Events other than 'not related' will be considered related in the clinical study report.

Not related: The event is most likely produced by other factors such as the subject's clinical condition, intercurrent illness, or concomitant medications or procedures and does not follow a known response pattern to the study device, or the temporal relationship of the event to study device administration makes a causal relationship unlikely.
Related: This relationship suggests that a reasonable temporal sequence of the event with device administration exists and, based upon known or previously reported adverse reactions to the device or class of devices or judgment based on the Investigator's clinical experience, the association of the event with the study device seems likely.

The severity (intensity) of AE will be graded according to the following definitions:
Mild: The subject experiences awareness of symptoms but these are easily tolerated or managed without specific treatment.
Moderate: The subject experiences enough discomfort to cause interference with usual activity, and/or the condition requires specific treatment.
Severe: The subject is incapacitated with inability to work or do usual activity and/or the event requires significant treatment measures.

An unexpected AE is one that is not consistent with the subject's past medical or acute burn history and is not evident from previous clinical experience with the test product or reasonably anticipated from pre-clinical information. An AE will be classified as 'serious' when it refers to any event during the 12-month study period that results in any of the following:

- Death
- Life-threatening adverse experience (i.e., the subject was at immediate risk of death from the reaction as it occurred)

- Inpatient hospitalization or prolongation of existing hospitalization
- Persistent or significant disability or incapacity
- A medically significant event or one requiring intervention to prevent one of the outcomes listed above and suspected to be due to the test product

All SAE will be followed until stabilization or improvement.

Clinical site personnel will be trained to follow study processes for reporting SAE. SAE reports will be managed by the clinical research team. The Principal Investigator will manage the process of ensuring that reports are completed appropriately and forwarded in a timely manner to all required recipients. The Principal Investigator will also assess individual and accumulating SAEs, AEs, and other safety data on a regular basis to identify any safety signals that should be brought to the attention of the Sponsor, , IRB offices, and/or the FDA.

Reporting for SAE which **are expected and not related** to KeraStat Gel will be as follows:

- The Principal Investigator (PI) will be notified within 24 hours of the Investigator becoming aware of any SAE that is expected or not related to the test product.
- The PI will promptly notify the Sponsor, the local IRB office and the central IRB office of all SAE.
- The Investigator will complete an SAE form and send it to all IRB offices and Sponsor within ten days of the SAE.

Reporting for an SAE that is determined to be **both unexpected and deemed related** to KeraStat Gel treatment will be as follows:

- SAE that are both unexpected and possibly or probably related to the test product will be reported within 24 hours of the Investigator becoming aware of the event via telephone, facsimile, or e-mail to the PI.
- The PI will notify the Sponsor, the local IRB office, and the central IRB office of all SAE within 72 hours of learning of the SAE.
- The Investigator will send the SAE report to all IRB offices and Sponsor within ten days of the SAE.
- The Sponsor will submit the SAE report to all Investigators and will submit the FDA MedWatch report to the FDA.
    - Within 7 calendar days for fatal or life-threatening SAE
    - Within 15 calendar days for all other unexpected and related SAE

Any unanticipated problems involving risks to subjects or others and AEs shall be promptly reported to the IRB, according to institutional policy. Reporting to the IRB is required regardless of the funding source, study Sponsor, or whether the event involves an investigational or marketed drug, biologic or device. Reportable events are not limited to physical injury, but include psychological, economic and social harm. Reportable events may arise as a result of drugs, biological agents, devices, procedures or other interventions, or as a result of questionnaires, surveys, observations or other interactions with research subjects.

All members of the research team are responsible for the appropriate reporting to the IRB and other applicable parties of unanticipated problems involving risk to subjects or others. The PI, however, is ultimately responsible for ensuring the prompt reporting of unanticipated problems involving risk to subjects or others to the IRB. The PI is also responsible for ensuring that all reported unanticipated risks to subjects and others that they receive are reviewed to determine whether the report represents a change in the risks and/or benefits to study subjects, and whether any changes in the informed consent, protocol or other study-related documents are required.

In order to ensure the safety, rights or welfare of research subjects any event, incident, experience, or outcome that alters the risk versus potential benefit of the research will prompt a substantive change in the research protocol or informed consent process/document.